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Euthyroid Sick Syndrome Is Predictive of Illness Severity in Pediatric Sepsis

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ABSTRACT

Background: Thyroid dysfunction, termed "euthyroid sick syndrome", was described in critically ill patients, but data in pediatric sepsis is limited.

Objective: Our objective was to evaluate prevalence and prognostic value of this syndrome among children with sepsis.

Patients and Methods: Prospective observational study including 81 children admitted into Pediatric Intensive Care Unit (PICU) with sepsis. Patients were classified on admission into "sepsis", "severe sepsis", and "septic shock" groups. Pediatric Index of Mortality2 (PIM2) was calculated. Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were measured upon PICU admission.

Results: Hormonal abnormalities were detected in 57 (70.4%) patients. 52 patients had FT3 deficiency; 7 had FT4 deficiency; 23 had TSH deficiency; and two had TSH elevation. The predominant pattern was isolated FT3 deficiency (32.1%) then combined FT3 and TSH deficiency (23.4%). Mean FT4 was lower among "septic shock" compared with "sepsis" and "severe sepsis" groups (p=0.001). TSH was lower among severe sepsis than sepsis (p=0.033). FT3, FT4, and TSH were lower among patients needing vasoactive medications (p=0.046, 0.037, and 0.022 respectively). TSH was lower among patients requiring mechanical ventilation (p=0.003). FT3, FT4, and TSH inversely correlated with vasoactive infusion days. TSH inversely correlated with mechanical ventilation duration and PIM2. No specific hormone was associated with mortality, but TSH predicted "unfavorable course" i.e., the composite outcome of mortality or presence of ≥ one illness severity indicator (area under receiver operating characteristic curve=0.70).

Conclusion: Euthyroid sick syndrome is common in pediatric sepsis. TSH and FT4 are particularly associated with illness severity.

Keywords: Euthyroid sick syndrome; Low T3 syndrome; Non-thyroidal illness syndrome; Prognosis; Pediatrics; Sepsis.

INTRODUCTION

In the setting of critical illness, abnormalities in thyroid function take place without prior intrinsic thyroid disease. Decreased serum triiodothyronine (T3) level is the most frequent alteration. Thyroxine (T4) level may also fall. Despite lowering of T3 and T4 levels, serum thyroid stimulating hormone (TSH) is normal or decreased. This constellation of abnormalities is termed "euthyroid sick syndrome" or "non-thyroidal illness syndrome" (NTIS). "Low T3 syndrome" is an alternative term, given the observation that low T3 level is the most striking and consistent finding. Euthyroid sick syndrome is thought to represent adaptive response, aiming at decreasing energy expenditure in sick patients[(1)].

Euthyroid sick syndrome has been reported in in acute conditions like pneumonia[(2)], sepsis[(3)], surgery, burn, and trauma[(4-6)]. Chronic illnesses, like collagen diseases, can also be associated with euthyroid sick syndrome[(7)].

How euthyroid sick syndrome develops in sepsis is not fully understood. It was suggested that pro-inflammatory cytokines (like interleukin-1, interleukin-6, interleukin-12, interleukin-18, and tumor necrosis factor-α) induce expression of deiodinase 1 in the pituitary and, possibly, induce expression of deiodinase 2 in both the hypothalamus and pituitary, that might be responsible for increased local availability of T3, which suppresses thyrotropin releasing hormone (TRH) and TSH secretion. Cytokines can also directly suppress TRH and TSH secretion. At the level of thyroid, cytokines affect different steps of thyroid hormone synthesis like iodide uptake and thyroid peroxidase expression, with consequent downregulation of T4 and T3 secretion. In peripheral tissues, deiodinase 3 expression is upregulated by cytokines and hypoxia, leading to conversion of T4 to the biologically inactive reverse T3 (rT3), while hepatic expression of the T3-producing enzyme deiodinase 1 is decreased. Furthermore, decreased thyroxine-binding globulin levels, altered thyroid hormone transporters, and altered thyroid hormone receptor expression may have a role in euthyroid sick syndrome[(8, 9)].

Interest in euthyroid sick syndrome has been growing, not only because of its ability to mislead doctors but also owing to its potential to predict prognosis in different clinical conditions [(2,5)]. However, available data on this condition in pediatric sepsis is very limited. Therefore, the aim of the present study was to determine the prevalence of euthyroid sick syndrome among pediatric patients with sepsis, and to evaluate its association with disease outcome.

SUBJECTS AND METHODS

This was a prospective observational study conducted on 81 patients with sepsis who were admitted to a tertiary Pediatric Intensive Care Unit (PICU) belonging to Menoufia University Hospital from October 2019 to April 2021.

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Patients and data collection

Critically ill children, aged 1 month to 16 years and diagnosed with sepsis, were eligible for inclusion in the study. Exclusion criteria included failure to measure hormone levels within 24 hours of PICU admission; pre-existent proven hypothalamic-pituitary-thyroid (HPT) axis abnormality; and suspicion of prior thyroid disease e.g., obesity, dry scaly skin, or constipation.

Patients were categorized on PICU admission as "sepsis", "severe sepsis", or "septic shock". Criteria for "sepsis" diagnosis were according to the international pediatric sepsis consensus conference[(10)], which requires the presence of systemic inflammatory response syndrome (SIRS) along with proven or suspected infection.

"Severe sepsis" was defined as sepsis plus acute respiratory distress syndrome (ARDS), cardiovascular dysfunction, or two other organ dysfunctions. "Septic shock" was defined as sepsis plus cardiovascular dysfunction.

Although "septic shock" is a subtype of "severe sepsis", it was considered a separate entity in the current study. Similarly, the subgroup "sepsis" did not include patients with "severe sepsis" or "septic shock".

The Pediatric Index of Mortality 2 (PIM2)[(11)] was calculated on admission for prediction of mortality. The pediatric Sequential Organ Failure Assessment (pSOFA) score was calculated at the end of the 1st 24 hours to determine the extent of organ dysfunction[(12)].

Laboratory investigations included complete blood count (CBC), C-reactive protein (CRP), and other routine investigations. Blood, urine, cerebrospinal fluid (CSF), and other body fluid cultures were taken to search for sepsis etiology.

Serum free T4 (FT4), free T3 (FT3), and TSH were measured within 24 hours of PICU admission by enzyme-linked fluorescent assay (ELFA), with a MINI VIDAS immunoanalyzer (bioMérieux, Marcy-l'Étoile, France). Hormone levels were deemed abnormal if they were $\leq 2.5^{th}$ percentile or $\geq 97.5^{th}$ percentile for age[(13)].

To allow identifying usual and unusual hormonal patterns, we defined euthyroid sick syndrome as any abnormality in FT3, FT4, or TSH in critically ill patients without prior HPT axis abnormality[(14)].

Management of septic shock was in accordance with American College of Critical Care Medicine guidelines[(15)]. Patients were followed up throughout their PICU stay. The primary outcome of the study was all-cause PICU mortality. The secondary outcome was the presence of "unfavorable course" which is a composite variable referring to the presence of one or more of the following: mortality, multiple organ dysfunction syndrome, requirement for mechanical ventilation, requirement for vasoactive medications, development of nosocomial infections, prolonged mechanical ventilation, prolonged vasoactive infusion days, or prolonged hospital stay.

Mechanical ventilation duration, PICU stay, and vasoactive infusion days were considered prolonged if they were > the median.

Ethical approval:

The Menoufia University's Ethics Committee gave this experiment its approval. Parents' written informed consents were acquired after being informed of the purpose of the study, and the data collected at the personal level was held in absolute confidence. The Helsinki Declaration was followed throughout the study's conduct.

Statistical methods

All calculations were performed by IBM SPSS (Statistical Package for the Social Sciences) version 23. Normally distributed continuous variables were presented as mean±standard deviation. Non-normally distributed continuous variables were expressed as median and interquartile range. Qualitative variables were shown as number and percentage. Chi-square or Fisher-exact tests were used to evaluate association between qualitative variables. t-test was used to compare the means between two groups while one-way analysis of the variance (ANOVA) was used for >two groups. Non-normally distributed continuous variables were compared by Mann-Whitney U test (for two groups) or Kruskal-Wallis test for >two groups. Correlations between variables were performed by Spearman correlation coefficient (r_s). Receiver Operating Characteristic (ROC) curve was used to assess performance of variables in predicting an outcome. All tests were bilateral and a p-value<0.05 was deemed statistically significant.

RESULTS

Characteristics of the study population

Eighty-one patients were recruited. Their clinical and baseline laboratory data are shown in table 1. Patients with severe sepsis and those with septic shock had significantly higher PIM2, pSOFA, mortality rate, mechanical ventilation rate, mechanical ventilation duration, and acute respiratory distress syndrome compared with those having sepsis. Patients with septic shock had significantly higher vasoactive infusion days compared with the sepsis group.

Blood culture was positive in 28 patients (34.1%). The source of sepsis was respiratory (63.9%), central nervous system (9.8%), gastrointestinal tract (4.9%), urinary tract (3.3%), cardiac (1.6%). No sepsis focus was detected in 16.5% of patients. No patient had Coronavirus disease 2019 (COVID-19) infection.

FT4 level was significantly lower in septic shock group compared with both sepsis and severe sepsis groups. TSH level was significantly lower in severe sepsis compared with the sepsis group (Table 1).

Table (1): Clinical and baseline laboratory data of the study population

Variable	Sepsis (Group A, n=43)	Severe sepsis (Group B, n=18)	Septic shock (Group C, n=20)	All patients (n= 81)	p-value	Groups significantly different
Age, month	18 (4 – 60)	17 (8 – 39)	10 (3 – 40)	16 (4- 48)	0.58	-
Male sex	18 (41.9%)	9 (50%)	9 (45%)	36 (44.4%)	0.84	-
Weight, Kg	9.5 (5- 17)	8 (6.5 – 11.8)	8.3 (4.4 – 14)	8.6 (5.5 – 15)	0.76	-
Malnutrition	14 (32.6%)	10 (55.6%)	7 (35%)	31 (38.3%)	0.23	-
Chronic comorbid conditions	18 (41.9%)	9 (50%)	7 (35%)	34 (42%)	0.65	-
PIM2 mortality risk%	1.9 (1.3 – 5.3)	7.1 (2.4 – 14.3)	7 (2.1 – 17.2)	2.8 (1.6 – 8.7)	0.001*	A-B, A-C
pSOFA score	3 (2 – 4)	7.5 (4.8 – 9.3)	7.5 (6 – 10.5)	4 (3 – 7)	<0.001 *	A-B, A-C
Mechanical ventilation	10 (23.3%)	14 (77.8%)	15 (75%)	39 (48.1%)	<0.001 *	A-B, A-C
Mechanical ventilation duration, days	0 (0 – 0)	4.5 (0.8 – 8.5)	4.5 (0.5 – 6)	0 (0 – 5)	<0.001 *	A-B, A-C
ARDS	1 (2.3%)	7 (38.9%)	4 (20%)	12 (14.8%)	<0.001 *	A-B, A-C
Vasoactive medication use	5 (11.6%)	6 (33.3%)	9 (45%)	20 (24.7%)	0.008*	A-C
Vasoactive infusion days	0 (0 – 0)	0 (0 – 3)	2.5 (0 – 5)	0 (0 – 0.75)	0.001*	A-C
PICU stay (among survivors), days	7 (5 – 10)	11 (7.5 – 17.5)	10 (5.5 – 28.3)	7.5 (5 – 12.3)	0.073	-
Mortality rate	3 (7%)	8 (44.4%)	12 (60%)	23 (28.4%)	<0.001 *	A-B, A-C
CRP, mg/dL	24 (6 – 48)	48 (11.5 – 82.5)	24 (2 – 48)	24 (6 – 48)	0.31	-
Hemoglobin, g/dL	9.8 (9.2 – 10.9)	9.8 (8.8 – 11.2)	10.4 (9 – 12.6)	10 (8.9 – 11)	0.56	-
WBC, 1000/µL	13.7 (9.5 – 21.5)	15.4 (7.9 – 21.2)	14.6 (5.9 – 20.2)	13.7 (8.3 – 20.6)	0.92	-
Platelets, 1000/µL	353 (176 – 436)	219 (69.5 – 358.5)	242 (88 – 343.5)	298 (146 – 382)	0.015*	A-B
Creatinine, mg/dL	0.5 (0.4 – 0.6)	0.55 (0.3 – 1.7)	0.75 (0.32 – 1)	0.5 (0.4 – 0.8)	0.29	-
ALT, U/L	24 (13.5 – 42)	24 (15.5 – 130.5)	15 (0.65 – 67.5)	22 (13.8 – 47.3)	0.22	-
FT3, pg/mL	2.30 (1.91 – 3.04)	2.43 (1.7 – 4.02)	2.20 (1.52 – 3.21)	2.30 (1.69 – 3.25)	0.64	-
FT4, ng/dL	1.28±0.31	1.36±0.33	0.98±0.23	1.22±0.30	0.001*	A-C, B-C
TSH, mIU/L	3.20 (0.81 – 3.90)	1.19 (0.57 – 2.23)	1.24 (0.77 – 2.44)	1.47 (0.72 – 3.55)	0.033*	A-B

Data are presented as median (interquartile range) if non-parametric test, as mean±standard deviation if parametric, or as frequency (percent) if categorical, ***:** Statistically significant

ARDS: Acute Respiratory Distress Syndrome**; PICU:** Pediatric Intensive Care Unit**; PIM2:** Pediatric Index of Mortality 2; **pSOFA:** pediatric Sequential Organ Failure Assessment score; **CRP:** C-reactive protein; **WBC:** White Blood Cell count; **ALT:** Alanine aminotransferase**; FT3:** Free triiodothyronine; **FT4:** Free thyroxine; **TSH:** Thyroid stimulating hormone.

Prevalence and patterns of euthyroid sick syndrome

Hormonal abnormalities were detected in 57 patients (70.4%). Low FT3 level was found in 52 patients (64.2%); low FT4 level in 7 patients (8.6%); low TSH level in 23 patients (28.4%); and high TSH in two patients (2.5%).

The predominant pattern of hormonal abnormalities was isolated decrease in FT3 level, followed by combined decrease in FT3 and TSH levels. The least frequent patterns were isolated FT4 deficiency and combined FT4 and TSH deficiency (Table 2).

Table (2): Types of hormonal abnormalities among the study population

Hormonal pattern	Number of patients	Percentage
Abnormal pattern	57	70.4%
Low FT3, normal FT4, normal TSH	26	32.1%
Low FT3, normal FT4, low TSH	19	23.4%
Low FT3, low FT4, normal TSH	5	6.2%
Normal FT3, normal FT4, low TSH	3	3.7%
Low FT3, normal FT4, high TSH	2	2.5%
Normal FT3, low FT4, low TSH	1	1.2%
Normal FT3, low FT4, normal TSH	1	1.2%
Normal pattern		
Normal FT3, FT4, and TSH	24	29.6%
Total	81	100%

FT3: Free triiodothyronine; **FT4:** Free thyroxine; **TSH:** Thyroid stimulating hormone

Hormone levels and chronic comorbid conditions

No significant difference in FT3, FT4, or TSH was found between patients with, and those without, chronic comorbid conditions.

No significant difference in FT3, FT4, or TSH was found between patients with, and those without, malnutrition.

Table (3): Hormone levels in different clinical conditions

Variable	Free T3, pg/mL	p-value	Free T4, ng/dL	p-value	TSH, mIU/L	p-value
Non-survivors **Survivors**	1.91 (1.36 – 3.25) 2.40 (1.92 – 3.25)	0.16	1.13±0.26 1.26±0.30	0.13	1.18 (0.68 – 2.64) 1.97 (0.73 – 3.67)	0.26
Vasoactive medications **No vasoactive medication**	1.80 (1.44 – 2.71) 2.41 (1.92 – 3.26)	0.046*	1.08±0.24 1.27±0.30	0.037*	0.88 (0.61 – 1.80) 2.21 (0.80 – 3.78)	0.022*
Mechanical ventilation **No mechanical ventilation**	2.11 (1.62 – 3.48) 2.41 (1.85 – 3.25)	0.66	1.17±0.28 1.27±0.31	0.24	1.08 (0.63 – 2.09) 3.02 (1.08 – 3.86)	0.003*
ARDS **No ARDS**	1.95 (1.26 – 3.87) 2.40 (1.85 – 3.16)	0.43	1.24±0.30 1.22±0.29	0.87	0.98 (0.57 – 1.89) 1.85 (0.80 – 3.65)	0.060
Malnutrition **No malnutrition**	2.40 (1.80 – 3.52) 2.30 (1.55 – 2.99)	0.19	1.26±0.30 1.20±0.28	0.59	1.30 (0.65 – 3.63) 1.79 (0.78 – 3.51)	0.37
Chronic comorbid conditions **No chronic comorbid conditions**	2.02 (1.59–2.79) 2.41 (1.98–3.30)	0.13	1.22±0.29 1.23±0.30	0.85	1.46 (0.80–3.52) 1.74 (0.71–3.63)	0.63

Data are presented as median (interquartile range) if non-parametric test, as mean±standard deviation if parametric.

***:** Statistically significant; **ARDS:** Acute Respiratory Distress Syndrome**; FT3:** Free triiodothyronine; **FT4:** Free thyroxine; **TSH:** Thyroid stimulating hormone

Euthyroid sick syndrome and mortality

FT3, FT4, and TSH were inversely correlated with vasoactive infusion days. TSH alone was inversely correlated with mechanical ventilation duration and PIM-2 score but positively correlated with platelet and total leucocytic counts (Table 4).

Table (4): Spearman correlation coefficient between hormones and other variables

Variable	FT3		FT4		TSH	
	r_s	p-value	r_s	p-value	r_s	p-value
PIM2	-0.07	0.57	-0.12	0.31	-0.35	0.002*
pSOFA	0.02	0.84	0.03	0.79	-0.18	0.12
Vasoactive infusion days	-0.27	0.037*	-0.35	0.007*	-0.28	0.033*
Mechanical ventilation duration	-0.001	0.99	-0.17	0.13	-0.30	0.007*
PICU stay (among survivors)	0.02	0.90	-0.23	0.09	-0.17	0.19
Bicarbonate	0.10	0.42	0.14	0.25	0.04	0.75
CRP	-0.15	0.20	-0.11	0.13	0.10	0.40
Creatinine	-0.12	0.28	0.06	0.58	0.05	0.67
ALT	-0.17	0.15	0.06	0.59	0.1	0.41
Total bilirubin	0.11	0.64	0.10	0.68	-0.3	0.19
Albumin	-0.06	0.81	0.04	0.87	-0.12	0.61
Hemoglobin	-0.11	0.34	-0.04	0.72	0.11	0.33
WBC	0.07	0.54	0.07	0.53	0.22	0.046*
Platelet count	0.11	0.35	0.04	0.73	0.25	0.023*
FT3	NA	NA	0.47	<0.001*	0.23	0.038*
FT4	0.47	<0.001*	NA	NA	-0.19	0.079

***:** Statistically significant

PIM2: Pediatric Index of Mortality 2; **pSOFA:** pediatric Sequential Organ Failure Assessment score; **PICU:** Pediatric Intensive Care Unit**; CRP:** C-reactive protein; **ALT:** Alanine aminotransferase**; WBC:** White Blood Cell count; **FT3:** Free triiodothyronine; **FT4:** Free thyroxine; **TSH:** Thyroid stimulating hormone; **r_s:** Spearman correlation coefficient; **NA:** Not applicable

Euthyroid sick syndrome and illness severity

TSH had a fair AUC of 0.70, while FT3 and FT4 had poor AUC for predicting "unfavorable course" in PICU. At a cutoff level ≤2.27 mIU/L, TSH had a sensitivity 68.3% and a specificity of 71.4% for prediction of unfavorable course (Table 5).

Table (5): Prediction of "unfavorable course" [a] by FT3, FT4, and TSH

Variable	AUC (95% CI)	p- value	Cutoff level	Sensitivity	Specificity
FT3, pg/ml	0.564 (0.43 – 0.70)	0.38	≤1.97	40%	81%
FT4, ng/dL	0.563 (0.42 – 0.71)	0.39	≤1.48	78.3%	38.1%
TSH, mIU/L	0.70 (0.57 – 0.82)	0.007*	≤2.27	68.3%	71.4%

*****Statistically significant

[a] "Unfavorable course" includes one or more of the following: mortality, multiple organ dysfunction syndrome, need for mechanical ventilation, need for vasoactive medications, development of nosocomial infections, prolonged mechanical ventilation duration, prolonged vasoactive infusion days, or prolonged hospital stay.

AUC: Area under the receiver operating characteristic curve; **CI:** Confidence interval**; FT3:** Free triiodothyronine; **FT4:** Free thyroxine; **TSH**: Thyroid stimulating hormone

DISCUSSION

In the present study, we have shown that euthyroid sick syndrome is common among children with sepsis, with a rate of 70.4%. Regrettable, many pediatricians are unaware of euthyroid sick syndrome and may misinterpret the results of abnormal thyroid function tests in critical illness. For example, low T3 and T4 may be put forward as an explanation for bradycardia in a certain patient, while in fact it is due to another cause like malnutrition, hypothermia, drug toxicity, or increased intracranial pressure.

Compared with previous literature, the frequency of euthyroid sick syndrome in our study is close to that reported by a study of pediatric sepsis[16]. However, a high rate of 100% was reported by three pediatric studies, two of them included patients with meningococcal sepsis[3, 17, 18]. Differences in patients' characteristics, criteria of sepsis diagnosis, or hormone assay could explain this discrepancy. Differences in sepsis severity can offer another explanation, as suggested by a pediatric study showing a parallel between thyroid hormone levels and central nervous system (CNS) infection severity[19].

The most common pattern of hormone abnormalities detected in the current study was isolated decrease in FT3 level, followed by combined decrease in FT3 and TSH, then combined decrease in FT3 and T4 levels. Another pediatric study reported low FT3; combined decrease in FT3 and FT4; and low TSH level in 52%, 48%, and 64% of patients with sepsis respectively but it did not report on the rate of combined hormonal abnormalities involving TSH[3].

Noteworthy, we detected TSH elevation with low FT3 in two patients, whereas TSH level, in euthyroid sick syndrome, is expected to be normal or low then rises later during recovery[20]. However, this is not always the case as TSH elevation was reported to occur for a brief period early in the stress of surgery, ameliorating the early decline in T3[4]. A similar situation might have existed in these two patients.

We also found that TSH level was significantly lower among patients with severe sepsis compared with those having sepsis, while FT4 was significantly lower in the septic shock compared with both the sepsis and severe sepsis groups. Furthermore, lower FT3, FT4, and TSH were associated with vasoactive medication requirement and were inversely correlated with vasoactive infusion days. It is possible that levels of thyroid hormones decreased simply secondary to illness severity in septic shock. However, it is equally tenable that the low thyroid hormone level was a factor that "caused" septic shock as it has been recently hypothesized that "myocardial hypothyroidism" plays a "causal role" in pathogenesis of myocardial dysfunction associated with septic shock. It was found that thyroid hormones increase myocardial contractility through acting at myocardial calcium ion cycling and at the contractile and sarcomeric myocardial proteins. Furthermore, thyroid hormones regulate the number and affinity of myocardial α- and β-adrenergic receptors, and activity of adenylate cyclase system. Accordingly, the inotropic response to β-adrenergic stimulation is decreased in hypothyroidism[21].

Additionally, lower TSH level, in the present study, was associated with mechanical ventilation rate and was inversely correlated with mechanical ventilation duration, which is consistent with another study wherein euthyroid sick syndrome was associated with prolonged mechanical ventilation[22].

On the other hand, we found no correlation between the length of PICU stay and FT3, FT4, or TSH, which is consistent with previous studies in pediatric sepsis[16] and critically ill children in general[23]. Conversely, others found that euthyroid sick syndrome was associated with longer PICU stay among critically ill children[24], children surviving meningococcal septic shock[18]; and mechanically ventilated adults[22].

We also found no association between FT3, FT4, or TSH and nosocomial infections, while lower T3 and T4 levels increased the risk of nosocomial infections in a study of critically ill children[24, 25]. If a relation is found between euthyroid sick syndrome and nosocomial infections, it will likely be an indirect one, through being associated with greater illness severity and prolonged PICU stay, with consequent higher liability to nosocomial infections. Since we found no correlation between thyroid hormones and PICU stay, it was natural to have no association with nosocomial infections.

Unlike their association with indicators of illness severity, euthyroid sick syndrome was not associated in the present study with mortality, which is consistent with an earlier pediatric study of meningococcal sepsis[17] and another study of critically ill adults[26]. Conversely, a study of pediatric sepsis found that both low T3 and low T4 were associated with mortality (odds ratio 24.7 and 3.1 respectively) [16], and another study of critically ill children found that combined decrease in T3 and T4 levels increased mortality risk 30 times[23]. Likewise, T3 had a fair AUC of 0.76 for mortality prediction among critically ill adults[27]. These discrepancies might have been resulted from heterogeneity of patients, timing of hormone measurement, or type of hormone assay (total versus free hormone levels). It is also possible that the small sample size in our study did not enable us to detect such an association with mortality since the p-values were relatively small.

Although euthyroid sick syndrome in the present study was not associated with mortality, TSH was inversely correlated with the mortality predictive score, PIM2. Similarly, a previous study of critically ill children demonstrated a correlation between another score, Pediatric Risk of Mortality II (PRISM II), and

T3 level measured just before death or PICU discharge, but not the level measured on admission[23].

Another indirect evidence pointing to association of euthyroid sick syndrome with mortality was the positive correlation we found between TSH and both platelet and white blood cell counts which are known prognostic factors in sepsis[25].

From a broader perspective, TSH showed a fair ability (AUC 0.70) to predict "unfavorable course", which is a composite variable combing mortality and indicators of illness severity. The optimal cutoff level was ≤2.27 mIU/L, which is considered in the normal range, suggesting that poor outcome might be expected in sepsis even if TSH level is not low.

As stated earlier, inflammation is thought to be a mechanism underlying euthyroid sick syndrome. However, we did not find correlations between the level of any hormone and the inflammatory marker CRP, but this could be explained by the slow rise of CRP, compared with the rapid changes in thyroid function in acute stress[4]. In contrast, a study of premature neonates found stronger correlation between CRP and FT3 in the second week of life, coinciding with the highest frequency of sepsis and low T3[28].

Overall, it is to be noted from our current findings that TSH and FT4 had stronger associations with disease severity compared with FT3. This is consistent with the recent pediatric[24] and adult[29] trials which suggested that the central component of euthyroid sick syndrome, caused by TSH suppression (as evidenced by low serum T4), is harmful, while the peripheral component (caused by inactivation of T3, as evidenced by decreased T3/rT3 ratio) is beneficial.

Although euthyroid sick syndrome has shown prominent association with patient outcome in numerous studies, it is still far from clear if thyroid hormone replacement to such patients will be beneficial[9]. Pediatric randomized controlled trials didn't show robust benefits. Moreover, they were conducted only on children with cardiac surgery, so their findings are difficult to generalize. Importantly, all pediatric trials examined T3 supplementation, which could suppress TSH secretion and delay recovery of pituitary TSH secretion. TRH infusion avoids this concern.

Limitations of the present study include the small sample size but previous studies of euthyroid sick syndrome in pediatric sepsis were similarly small. Therefore, a meta-analysis or a multicenter study is needed. In addition, we did not repeat thyroid hormone measurements during PICU stay. We also did not exclude patients given medications that affect thyroid function like glucocorticoids, dopamine, and opiates, phenytoin, and phenobarbital[30].

Nevertheless, most of our patients did not receive these medications; dopamine, for example, is no longer the first-line vasoactive medication and is rarely used in our unit. Finally, we did not exclude patients with pre-existent chronic illness or malnutrition, but this appears not to have influenced our findings as no significant difference in hormone levels was found between these patients and other patients.

CONCLUSION

Euthyroid sick syndrome is common in pediatric sepsis and should be born in mind while evaluating such patients. TSH and FT4 had more prominent associations with illness severity compared with FT3. Lower FT4 was associated with septic shock and vasoactive medications. Lower TSH was associated with severe sepsis, mechanical ventilation, and vasoactive medications. Lower FT3 was associated only with vasoactive medications. No specific hormone was associated with mortality, but TSH fairly predicted "unfavorable course", that is, occurrence of mortality or presence of one or more indicators of illness severity. Furthermore, TSH showed indirect link to prognosis through its correlation with the mortality predictive score PIM2 as well as platelet and white blood cell counts, which are markers of poor prognosis.

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